Plasma Cell Dyscrasias & The Kidney

Brainstorming The Concept

Nephrology Perspectives

Mohammed Abdel Gawad

Nephrology Specialist

Kidney & Urology Center (KUC) - Alexandria

drgawad@gmail.com

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28, Jul, 2016

Amyloidosis

Multiple Myeloma

Imunotactoid GN

Fibrillary GN

Gamma Globulin

Dyscrasias

Monoclonal vs Polyclonal

Light vs Heavy Chain

Gammopathy

SPE / Immunofixation

LCDD, HCDD

Dyscrasia

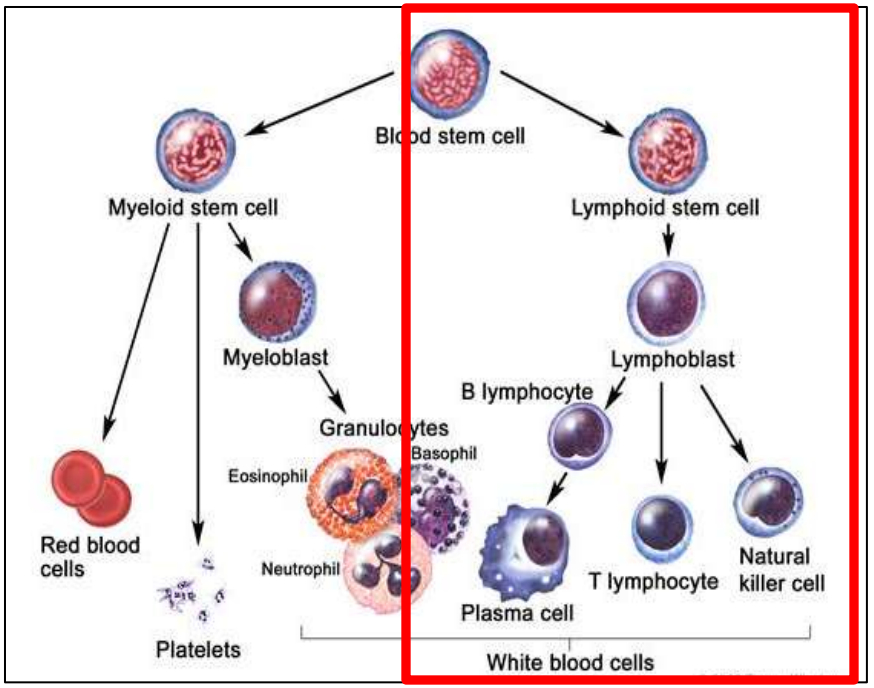
is a concept from ancient Greek medicine, meaning **bad mixture**

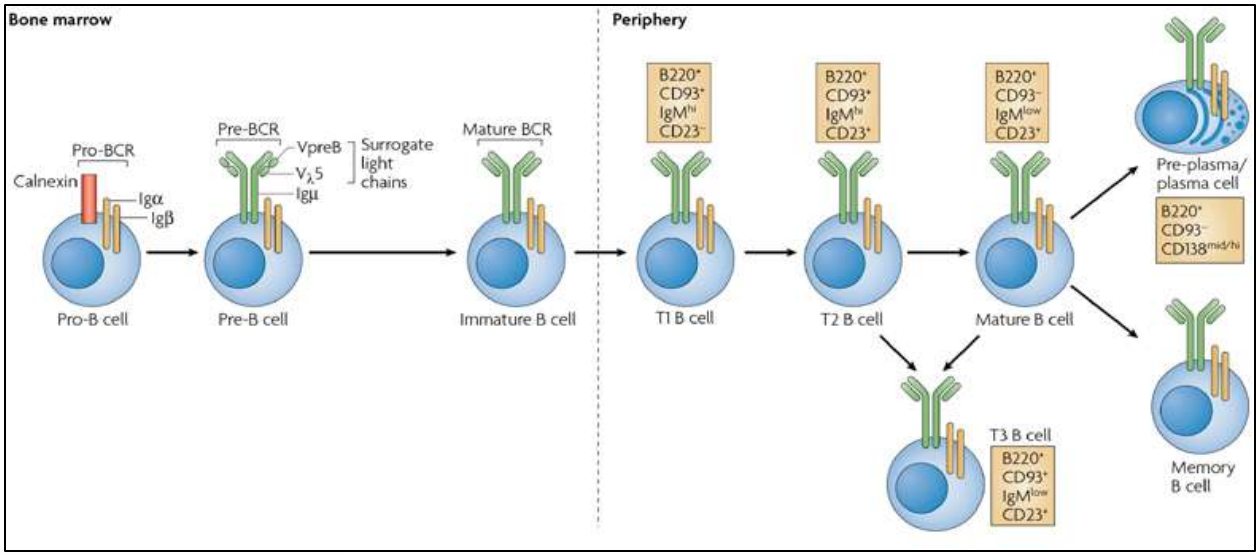
What is meant by Plasma Cell Dyscrasias?

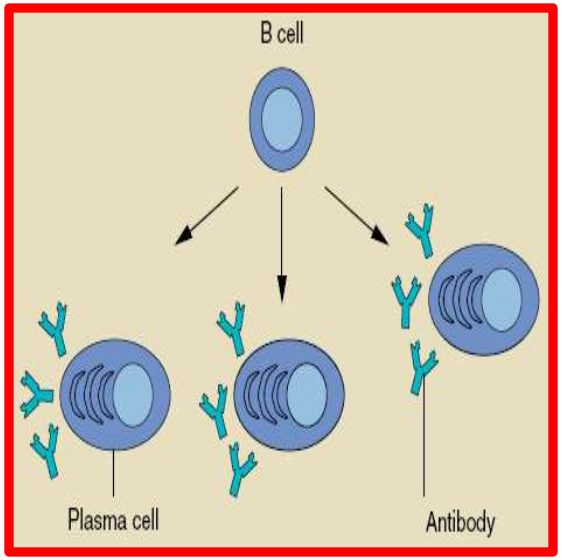
Bone marrow-derived malignant plasma cells → produce abnormal immunoglobulin proteins → that can cause renal injury by a number of mechanisms.

Plasma Cells

- Plasma cells ultimately originate in the bone marrow; howevaer, these cells leave the bone marrow as B cells, before terminal differentiation into plasma cells normally in lymph nodes.
- They are the primary mediators of humoral immunity, secreting antigen-specific immunoglobulins

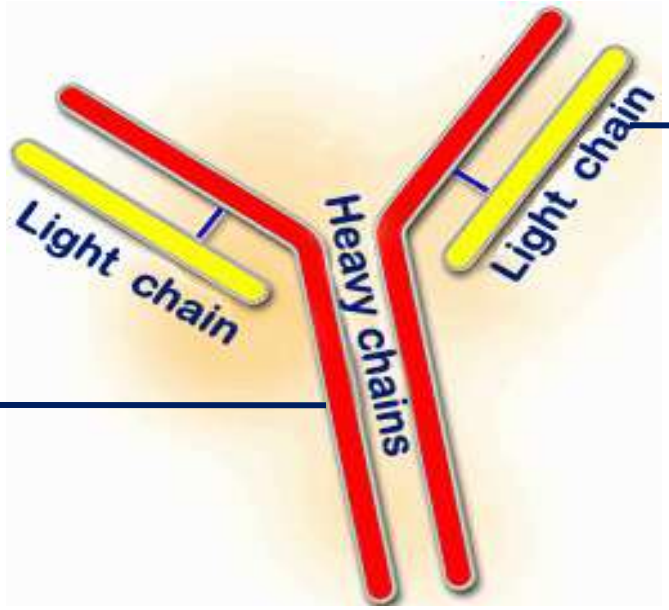






- Fairfax KA, Kallies A, Nutt SL, et al. Semin Immunol. 2008;20:49
- Radbruch A, Muehlinghaus G, Luger EO, et al. Nat Rev Immunol. 2006;6:741-750.

Immunoglobulin (Antibody, Gama Globulin) Structure



kappa (κ) or lambda (λ)

IgM, IgA, IgG, IgE, IgD

Kolitha Basnayake et al. Kidney International (2011) 79, 1289–1301

Monoclonal Abs (Ig, Gama Globulin)

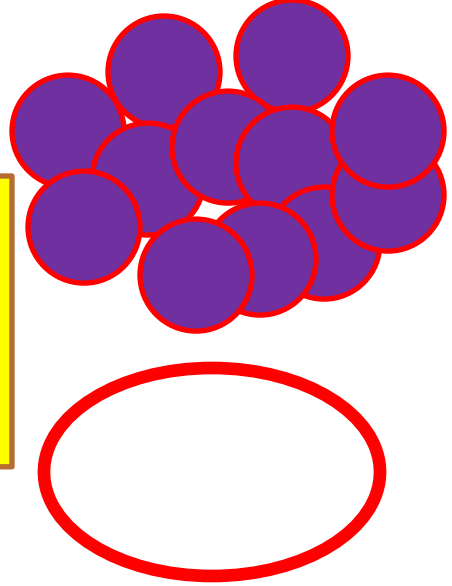
Polyclonal Abs (Ig, Gama Globulin)

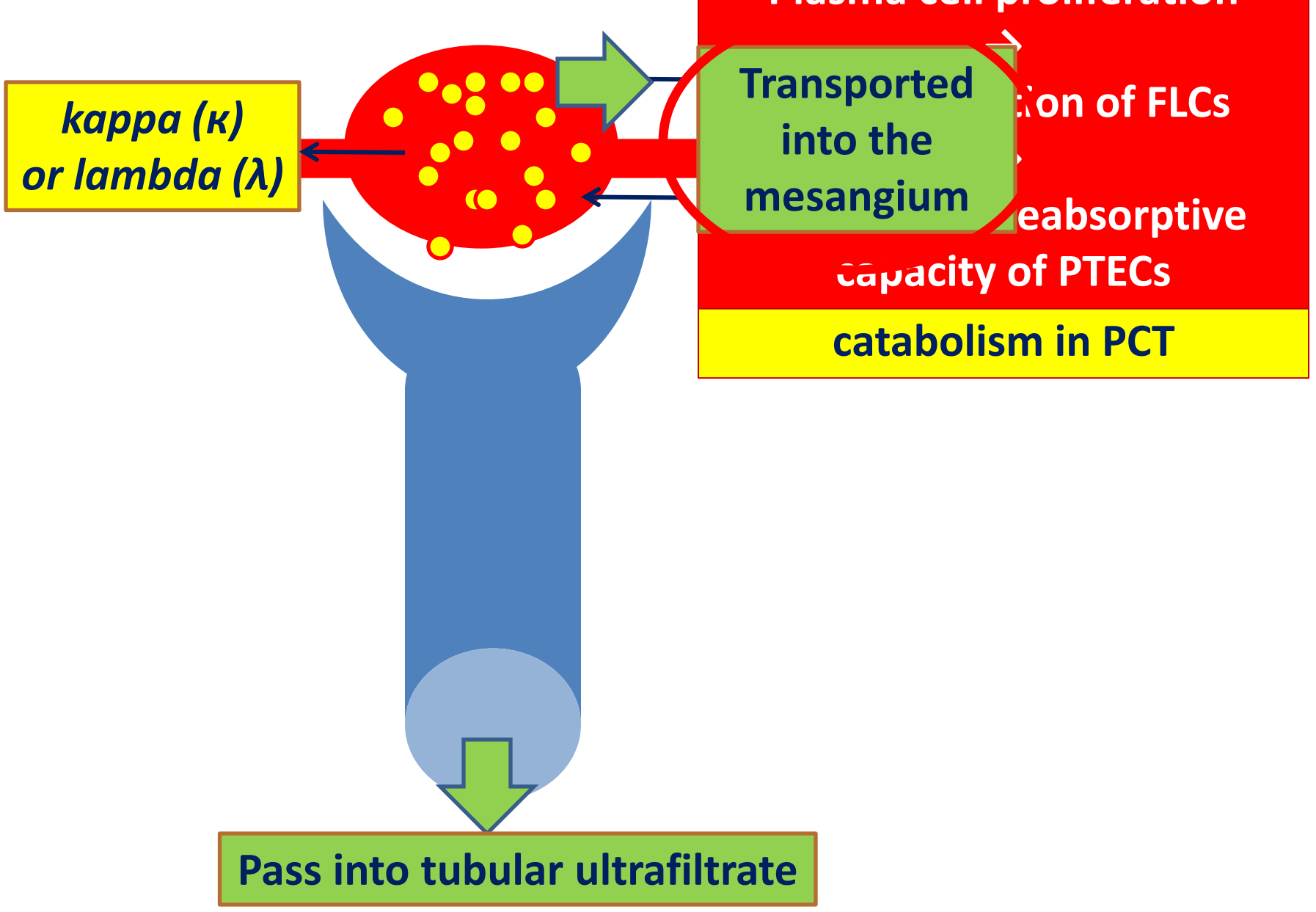
• Fairfax KA, Kallies A, Nutt SL, et al. Semin Immunol. 2008;20:49
• Radbruch A, Muehlinghaus G, Luger EO, et al. Nat Rev Immunol. 2006;6:741-750.

Plasma Cell Dyscriasis

(Clonal proliferation of plasma cells)

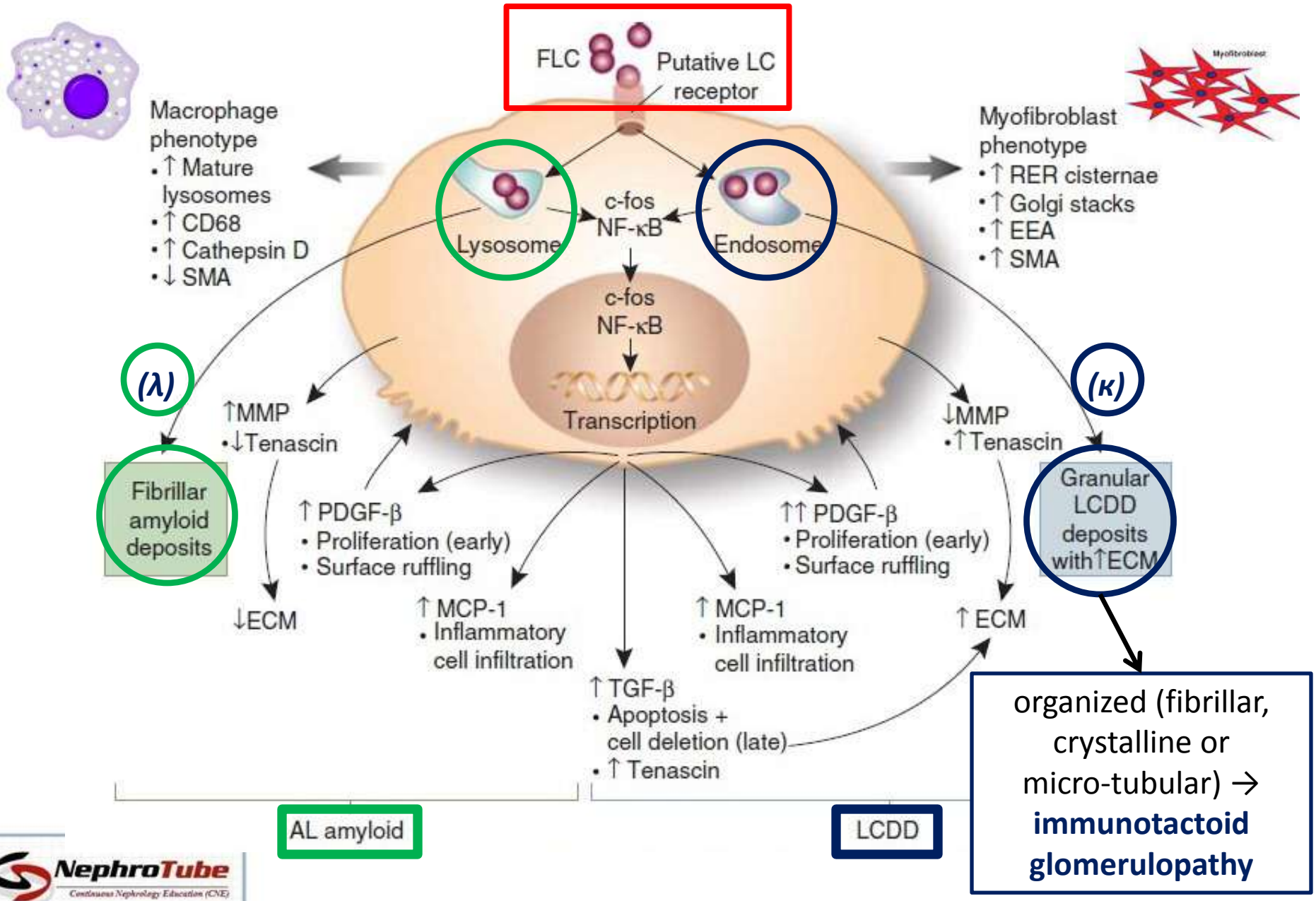
How they affect the kidney?





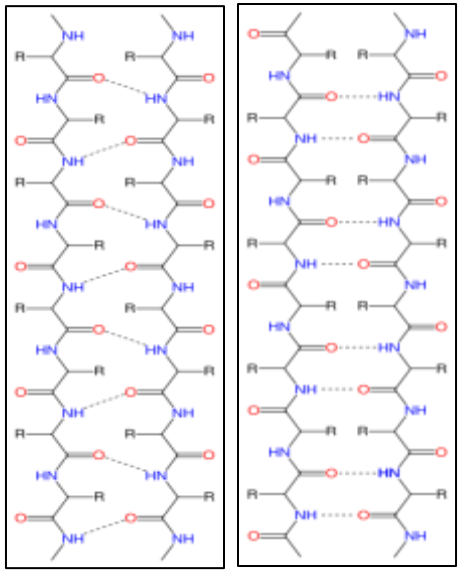
Kolitha Basnayake et al. Kidney Int (2011) 79, 1289–1301
Maack T et al. Kidney Int 1979;16: 251–270.
M. Gawad. www.NephroTubeCNE.com

Interactions of FLCs with mesangial cells (MCs): AL amyloidosis (left) and light chain deposition disease (LCDD; right).



Kolitha Basnayake et al. Kidney Int (2011) 79, 1289–1301

Primary (AL) Amyloidosis



Antiparallel β-Sheets

Parallel β-Sheets

FLC (λ)

Serum amyloid protein (SAP)

Protects fibrils from proteolytic degradation

Glycosaminoglycans (Heparan sulfate)

Fibrillar amyloid deposits

Fibrillary, misfolded, nonbranching, β-pleated sheet structures (7-12nm)

major site in glomeruli, with arterioles, arteries, interstitium, and tubular basement membranes involved to lesser degrees.

AL amyloid

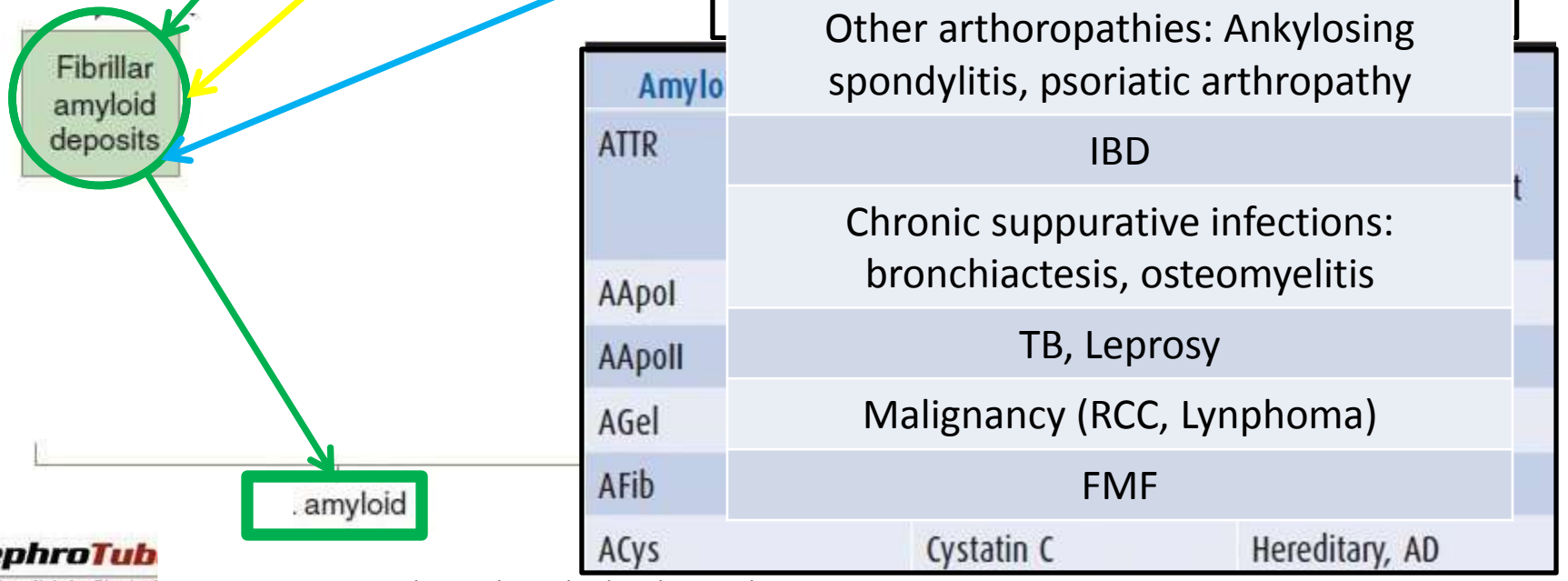
Herrera GA, et al. Ultrastruct Pathol 1999; 23: 107–126.
Herrera GA. Ann Diagn Pathol 2000; 4: 174–200.
Tennent GA et al. Proc Natl Acad Sci USA 1995; 92: 4299–4303.
Scholefield Z et al. J Cell Biol 2003; 163: 97–107.
Yamaguchi I et al Kidney Int 2003; 64: 1080–1088.

Primary (AL) Amyloidosis

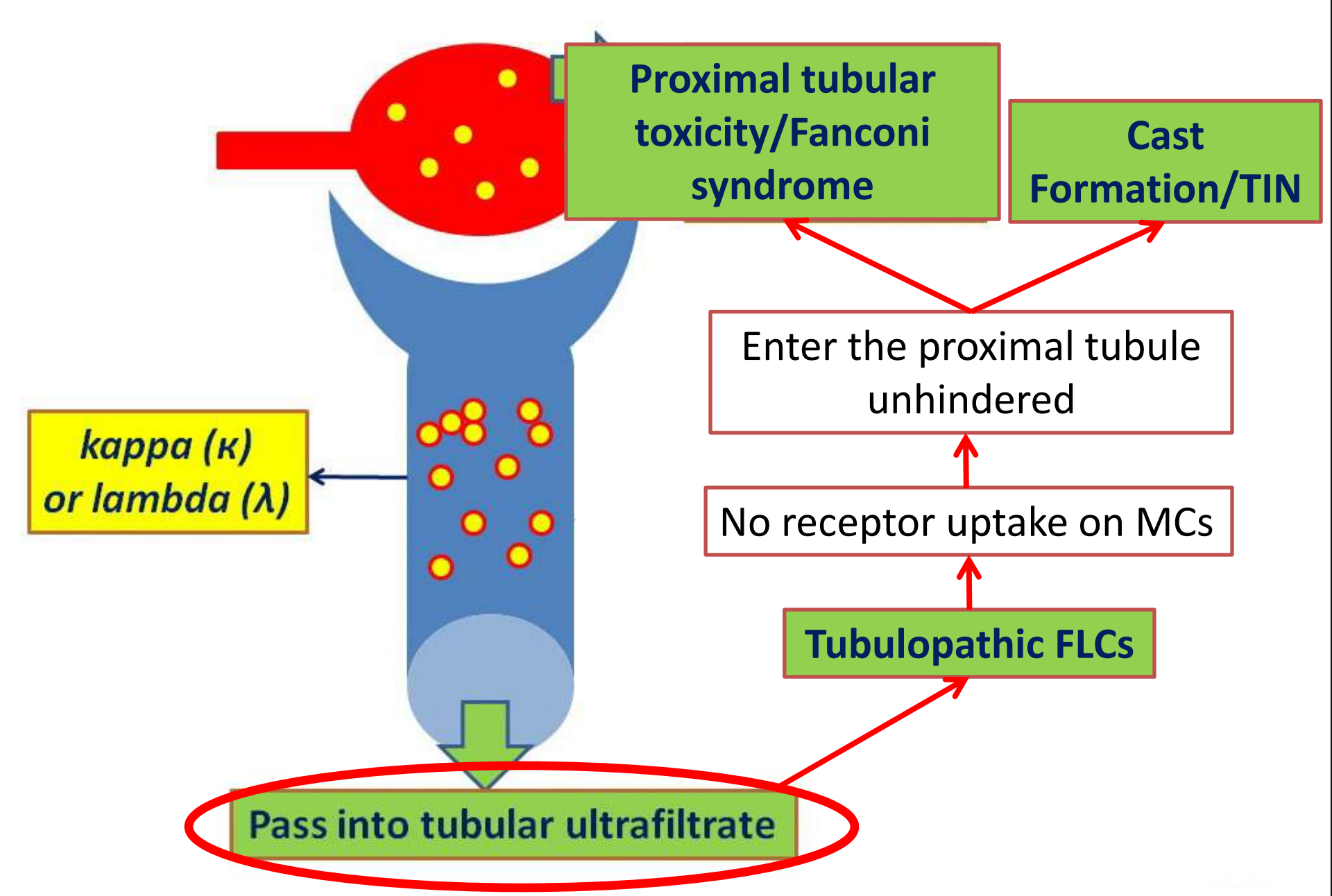
Secondary (AA) Amyloidosis

Fibrils are composed of the **serum Amyloid A** protein.

Causes of AA
Rheumatoid arthiritis
Other arthoropathies: Ankylosing spondylitis, psoriatic arthropathy
IBD
Chronic suppurative infections: bronchiactesis, osteomyelitis
TB, Leprosy
Malignancy (RCC, Lynphoma)
FMF



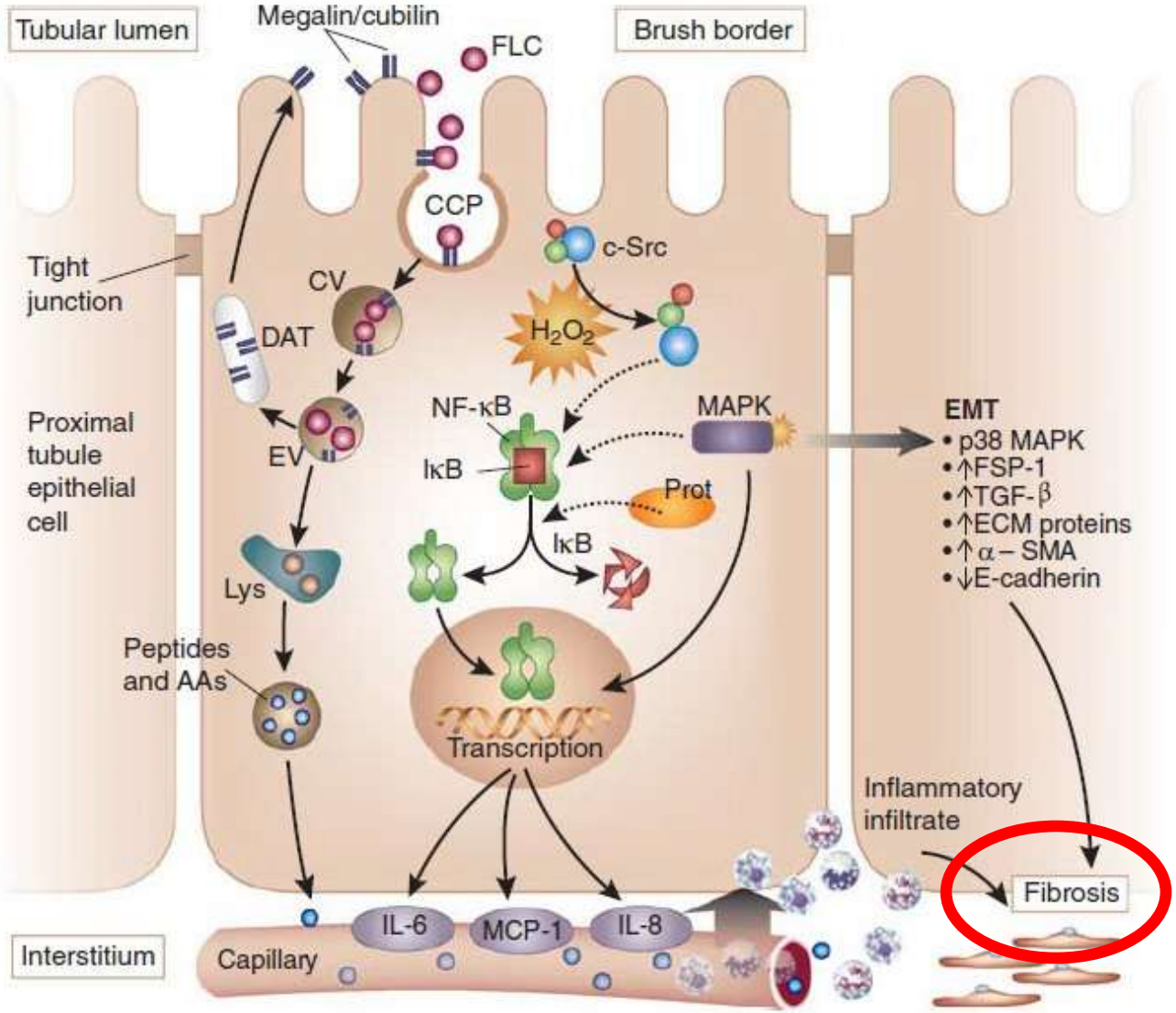
Novak L et al. Nephrol Dial Transplant 2004;19:3050.
Jaccard A. Moreau P, Leblond V, et al. N Engl J Med 2007; 357 (11): 1083–1093.



Kolitha Basnayake et al. Kidney Int (2011) 79, 1289–1301
Maack T et al. Kidney Int 1979;16: 251–270.

Figure 2 | Interactions of free light chains (FLCs) with proximal tubule epithelial cells (PTECs).

The classical histological finding is intralysosomal crystalline deposits of FLCs within PTECs



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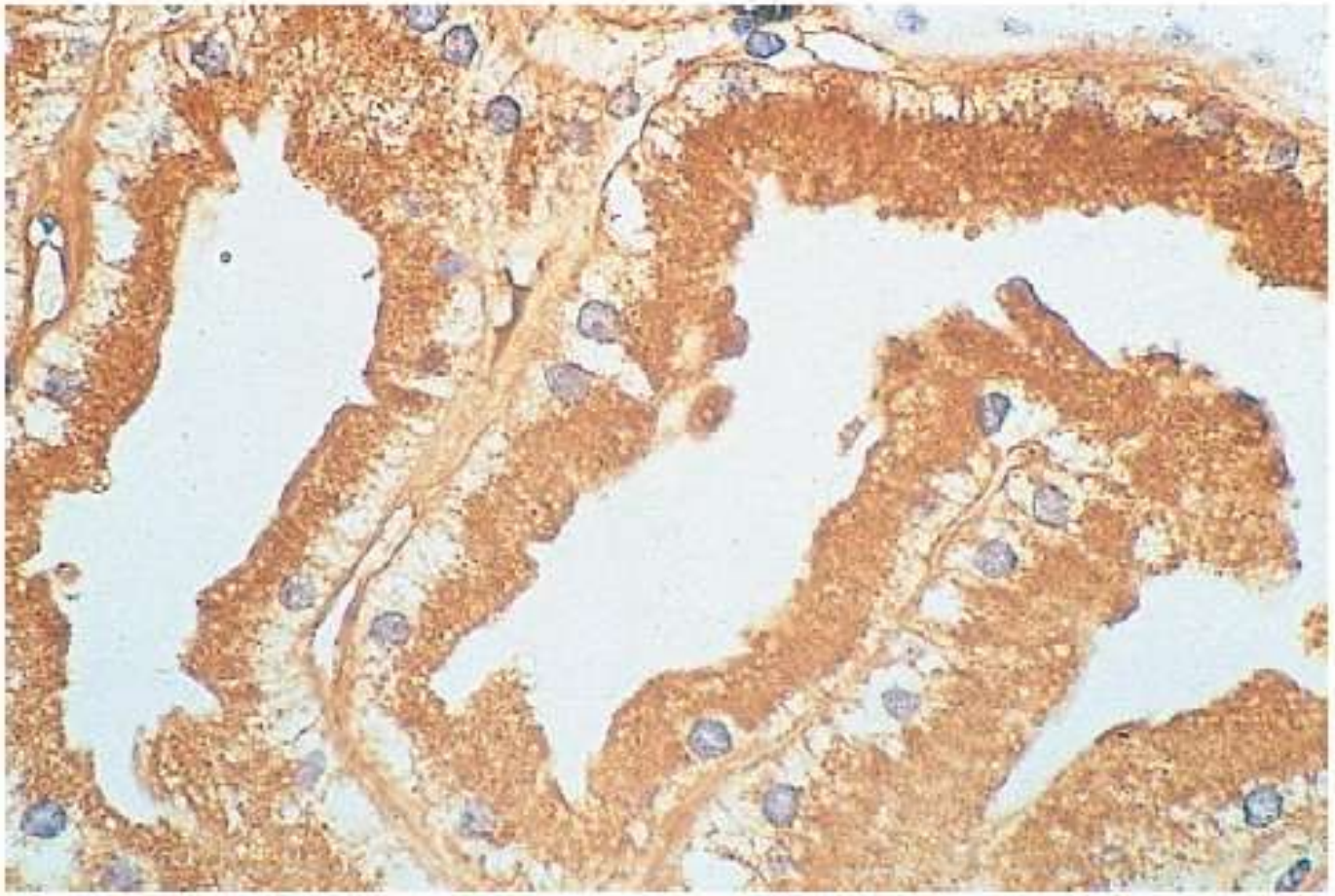


Figure 63.2 Uptake of light chains by proximal tubular cells. Renal biopsy specimen from a patient excreting κ light chains. Immunoperoxidase staining showing κ light chains along the brush border and in the cytoplasm of the PTC (brown stain).

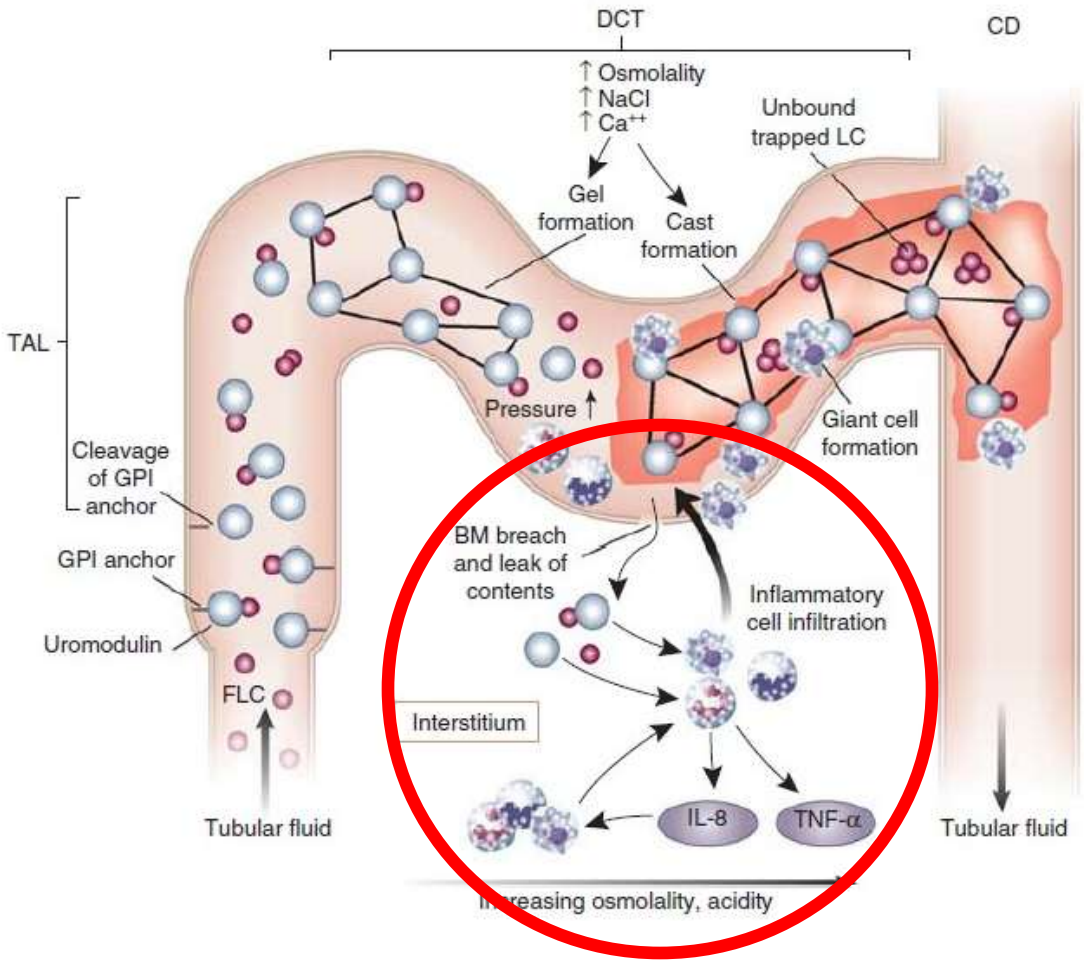
Ashley B. Irish . Comprehensive Clinical Nephrology. 5th edition, chapter 65.

Figure 3 | Light chain interactions in the distal nephron.

Fractured **DCT** protein precipitates (casts), consisting of **uromodulin & FLC**

Cast formation is **characteristic** for **Multiple Myeloma**.
But it may also be seen in up to a **third of cases of LCDD**, but is **rare in AL amyloidosis**

Cast is characterized by **tubulointerstitial inflammation and fibrosis**



Kolitha Basnayake et al. Kidney Int (2011) 79, 1289–1301
Pozzi C et al. Am J Kidney Dis 2003; 42: 1154–1163.

When to suspect Amyloidosis clinically ?

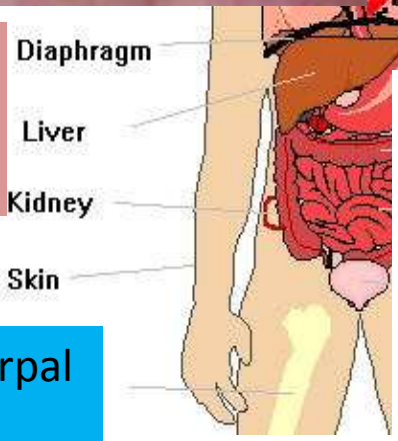
Nephrotic syndrome

(severe edema, often with anasarca and pleural effusions)

Pierre M. Ronco. Comprehensive Clinical Nephrology. 4th edition, chapter 26.

ure 26.6 Macroglossia in a patient with AL amyloidosis. (Co

Hepatomegaly
Easy bruising, Factor IX and X deficiency with bleeding



Peripheral neuropathy (carpal tunnel syndrome)

Involvement of the primary h

Figure 26.7 Skin involvement in AL amyloidosis. Noninfiltrated purpuric macule of the superior eyebrow, very typical of AL amyloidosis.

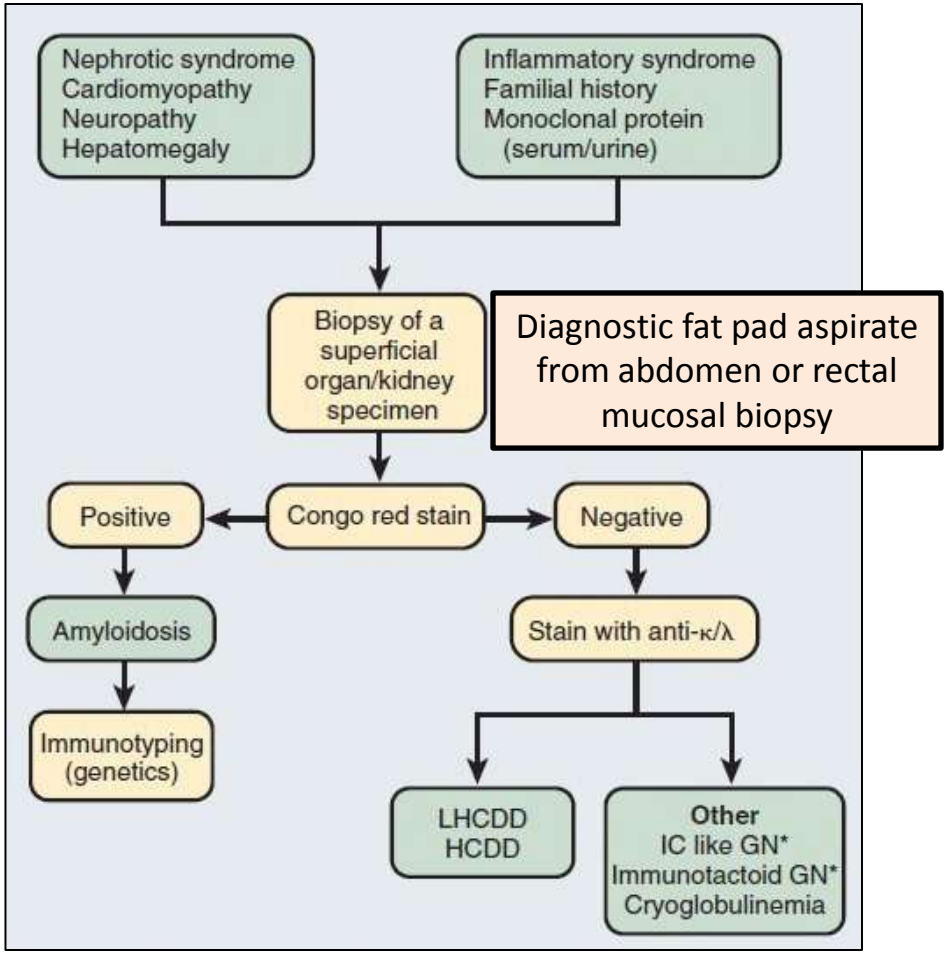
Pierre M. Ronco. Comp

When to suspect LCDD Clinically?

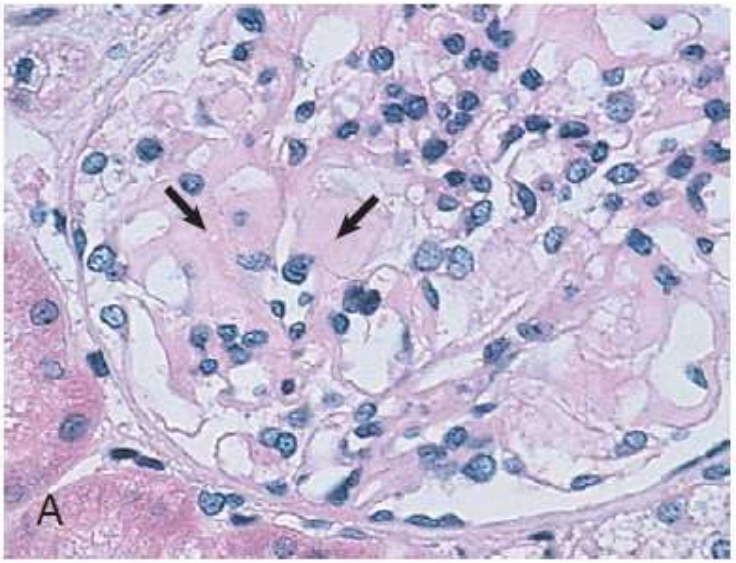
Clinical Features in Patients with MIDD		
Characteristics	**LCDD/LHCDD**	**HCDD**
Male-to-female ratio	1.5	0.7
Age, yr (range)	57 (28-94)	56 (26-79)
Hypertension (%)	53	90
Renal failure (serum creatinine ≥130 µmol/l) (1.47 mg/dl) (%)	93	85
Nephrotic syndrome* (%)	35	50
Hematuria (%)	45	88
Nodular glomerulosclerosis (%)	31-100	96
Multiple myeloma (%)	52	22
Monoclonal protein (blood or urine) (%)	84	56†

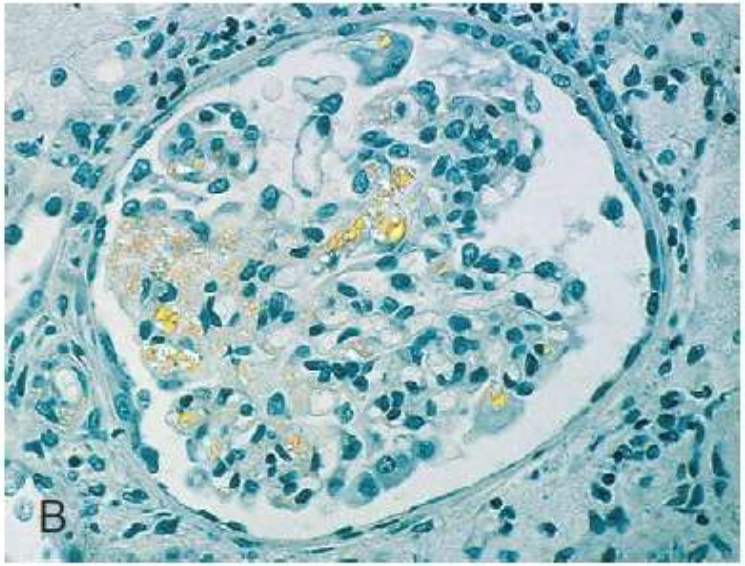
Pierre M. Ronco. Comprehensive Clinical Nephrology. 5th edition, chapter 27.

Stepwise Approach - AL Amyloidosis or LCDD Diagnosis?



Pierre M. Ronco. Comprehensive Clinical Nephrology. 5th edition, chapter 27.





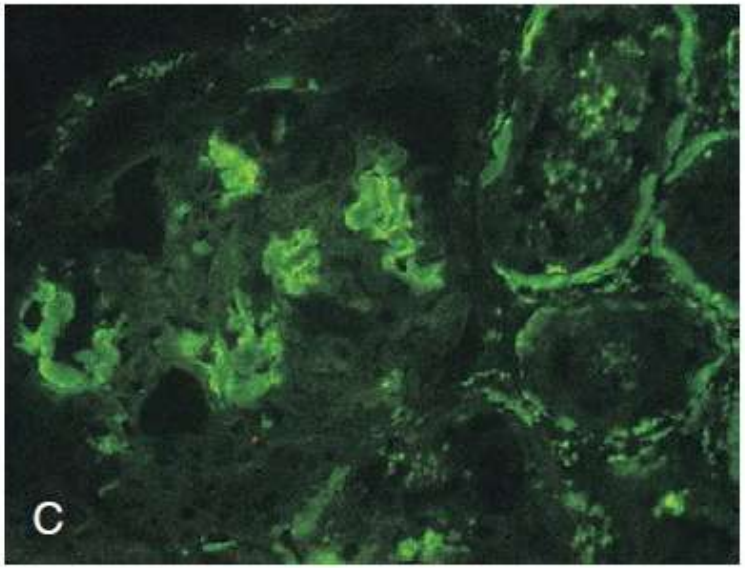
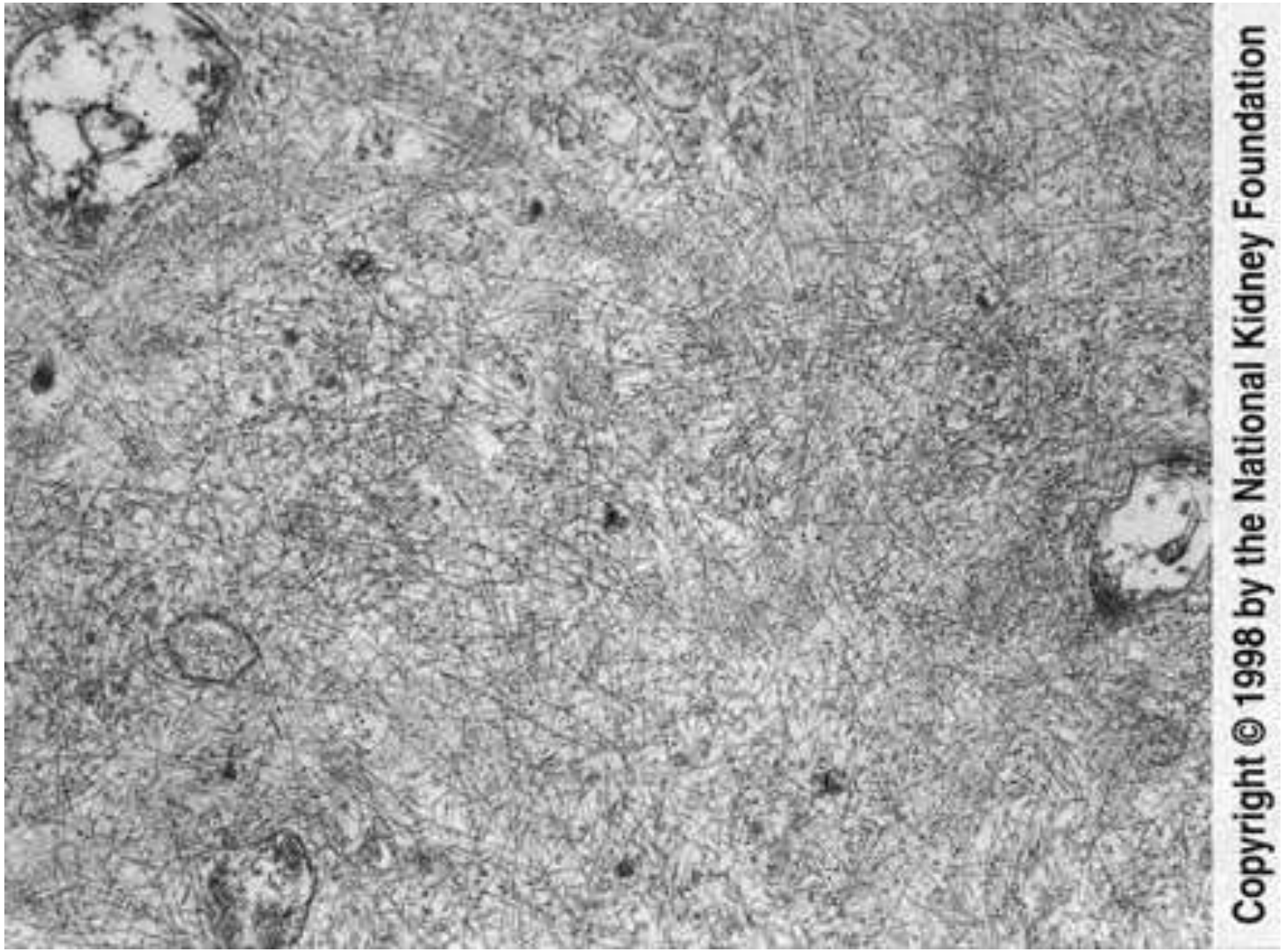


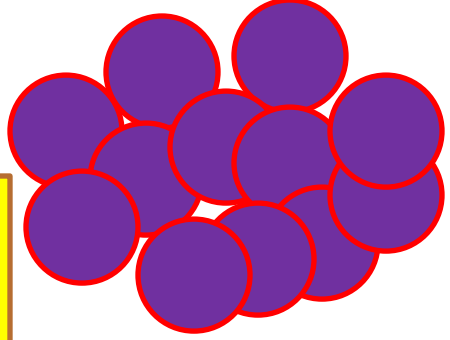
Figure 26.3 **Amyloidosis. A,** Amyloid deposits *(arrows)* in a glomerulus. (Hematoxylin-eosin; magnification ×312.) **B,** Congo red staining. Apple-green birefringence under polarized light. (Magnification ×312.) **C,** Immunofluorescence with anti-κ antibody. Note glomerular and tubular deposits. (Magnification ×312.) *(Courtesy Dr. Béatrice Mougenot, Paris, France.)*

Pierre M. Ronco. Comprehensive Clinical Nephrology. 5th edition, chapter 27.



By electron microscopy, amyloid appears as randomly oriented thin fibrils, 10 to 12 nm in diameter, with a loose, flocculent background (transmission electron microscopy; original magnification x51,250).

How they affect the kidney?



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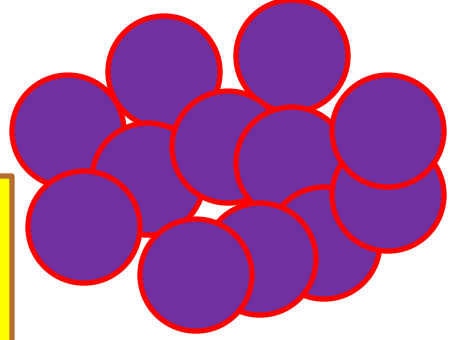
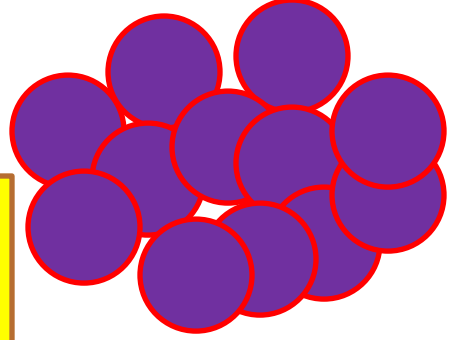


- **Plasma Cell Dyscriasis** (Clonal proliferation of plasma cells)
  - **Monoclonal gammopathy** (Paraproteinemia)
    - Excess monoclonal LIGHT chain
      - Mainly λ
        - Amyloid fibril transformation (fibrils 8-15 nm)
          - AL (primary amyloidosis
      - λ or κ
        - Immunotactoid GN (glomerulonephritis with organized monoclonal microtubular immunoglobulin deposits GOMMID) (microtubules >30nm)
      - Mainly κ
        - LCDD (granular deposits
    - Excess monoclonal HEAVY chain
      - HCDD (granular deposits)
      - HLCDD (λ or κ) (granular deposits)
    - Excess monoclonal INTACT Ig
  - **Polyclonal gammopathy**

How they affect the kidney?



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        - LCDD (granular deposits
    - Excess monoclonal HEAVY chain
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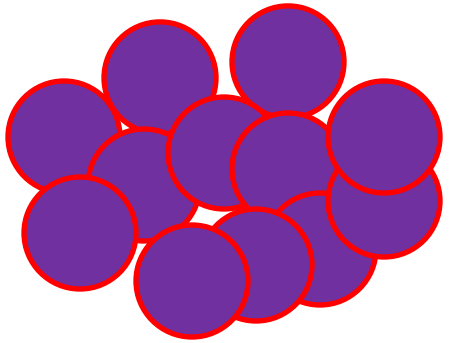
  - **Polyclonal gammopathy**
    - Excess monoclonal INTACT Ig

What is Multiple Myeloma?

Excess of bone marrow–derived plasma cells

- Dysregulated overproduction of a monoclonal Ig (the paraprotein or M-protein)
- Associated light chains (kappa and lambda)



Leung N et al. Am J Kidney Dis 2004;43:147.
Pozzi C et al. Am J Kidney Dis 2003;42:1154.

When to suspect Multiple Myeloma?

International Myeloma Foundation
Improving Lives • Finding the Cure®

	MGUS	Smouldering (asymptomatic) myeloma	Active (symptomatic) myeloma
Serum M-protein	<3 g/100ml	≥3 g/100ml	≥3 g/100ml
Bone marrow clonal plasma cells	<10%	≥10%	≥10% or Plasmacytoma
Related organ or tissue impairment	Absent and No evidence of other B-cell proliferative disorders	Absent/ Asyptomatic	Requires 1 or more of the following: • **C**alcium elevation • **R**enal insufficiency • **A**naemia • **B**one osteolytic lesion

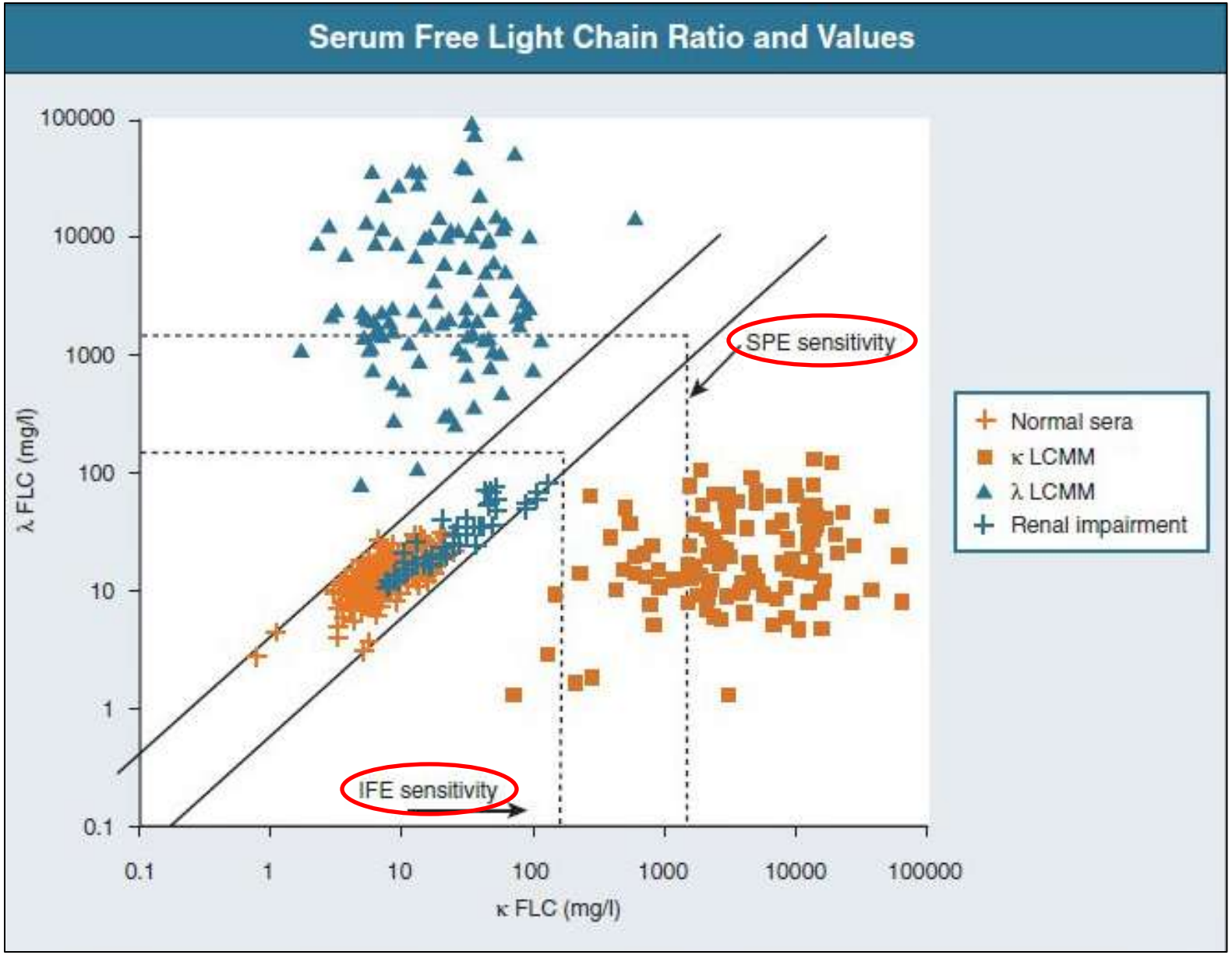
NephroTube
Continuous Nephrology Education (CNE)
www.NephroTubeCNE.com

International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003;121:749-757.

Laboratory Diagnostic Tests

Serum protein electrophoresis (SPE)	Serum immunofixation electrophoresis (sIFE)
Can detect the whole immunoglobulin *(cannot reliably differentiate monoclonal from polyclonal light chain expansion)*	10 times more sensitive for immunoglobulins

Katzmann JA et al. Clin Chem. 2002;48(9):1437-1444.

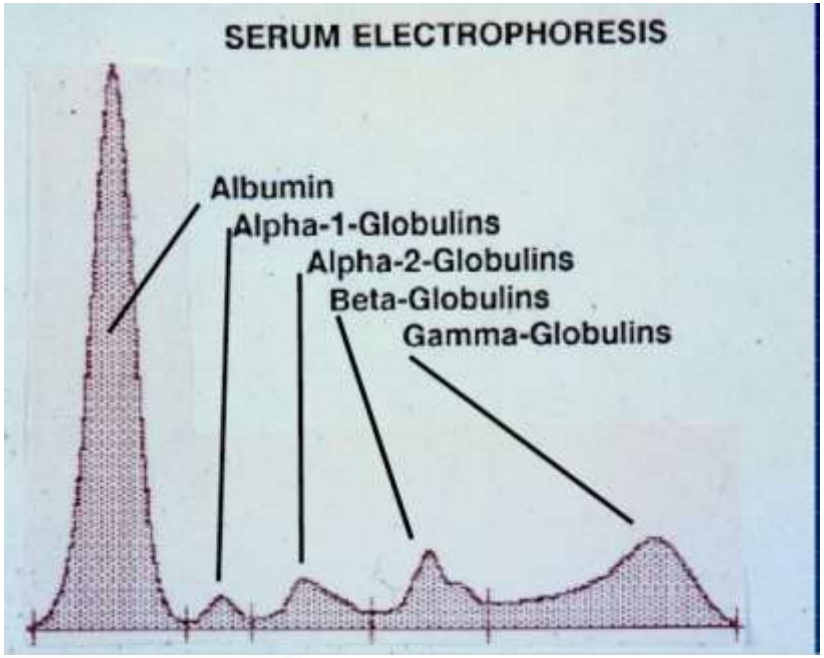


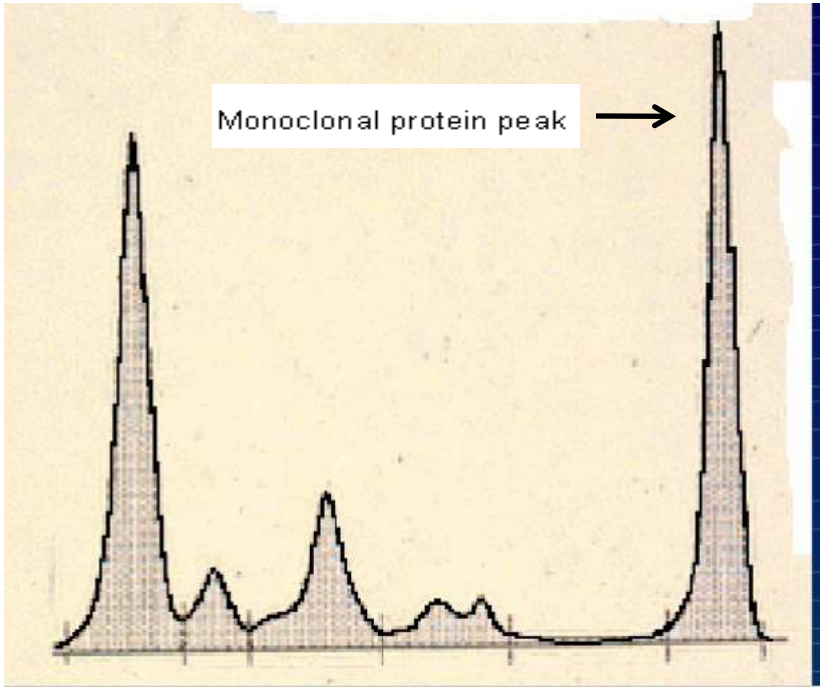
Ashley B. Irish . Comprehensive Clinical Nephrology. 5th edition, chapter 65.

Serum protein electrophoresis (SPE)

Paraprotein is

a monoclonal Ig (gamma globulin)
that is produced in excess
by the clonal proliferation of plasma cells.





Katzmann JA et al. Electrophoresis. 1997;18:1775-1780.

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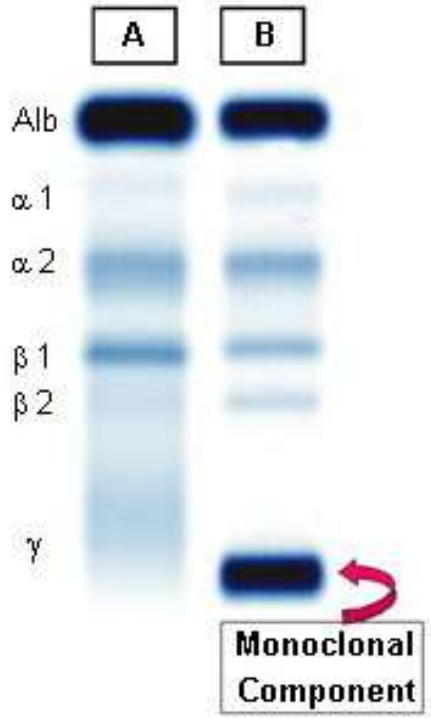


Laboratory Diagnostic Tests

Urine PEP, immunofixation electrophoresis (uIFS) *(to detect Bence Jones Proteinuria)*	Serum PEP, immunofixation electrophoresis (sIFE)

Dr. Henry Bence-Jones
31 December 1813 / / April 20, 1873

Serum Free Light Chains (κ and λ) Measurement

By Nephelometry

along w ... *myloidosis,*

This excess is detectable in the serum in MIDD, amyloid, or "nonsecretory" myeloma, in whom no monoclonal Ig has been identified with electrophoretic techniques.

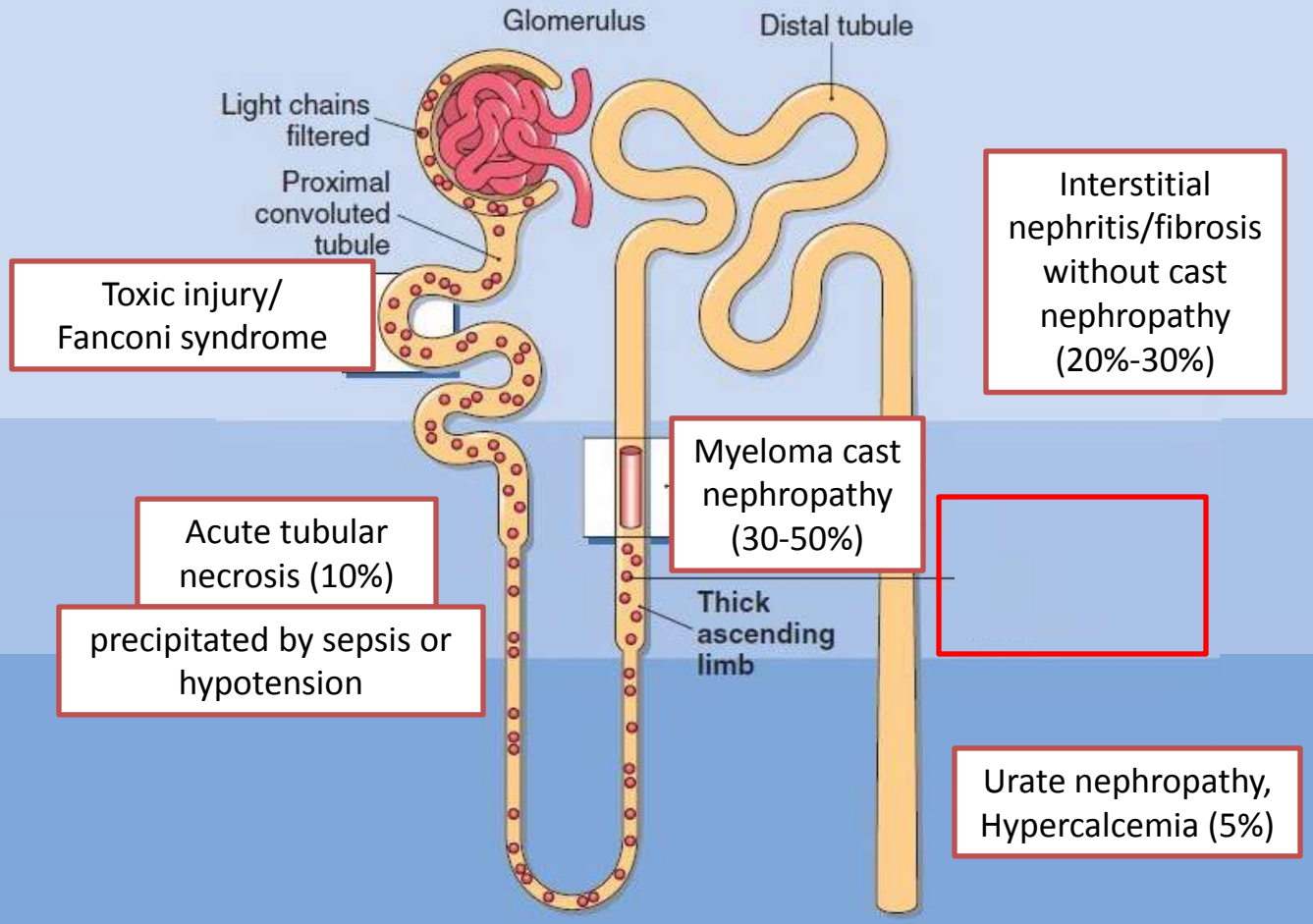
... /λ ratio

- Serial measurements help to monitor therapeutic response.
- Advocated by the International Myeloma Working Group (IMWG) for initial screening of plasma cell dyscrasias.

This excess is detectable in the serum before urinary tubular catabolism is exceeded and before the SPE or IFE is abnormal

Katzmann JA et al. Clin Chem. 2002;48(9):1437-1444.
Lachmann HJ et al. Br J Haematol. 2003;122(1):78-84.

How Multiple Myeloma affect the Kidney?



Ashley B. Irish . Comprehensive Clinical Nephrology. 5th edition, chapter 65.
Korbet SM. J Am Soc Nephrol 2006;17:2533.
San Miguel JF et al. N Engl J Med 2008;359 (9): 906–917.

Renal Pathology in Patients with Multiple Myeloma

Histological Finding	Prevalence
Myeloma kidney *(Myeloma cast nephropathy)*	30%-50%
Interstitial nephritis/fibrosis without cast nephropathy	20%-30%
Amyloidosis	10%
Light chain deposition disease	5%
Acute tubular necrosis	10%
Other (urate nephropathy, tubular crystals, hypercalcemia, FSGS)	5%

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	Myeloma Kidney	Other MIDDs
Proteinuria	<3 g/l	>3 g/l
Hematuria	Rare	LCDD, occasional Amyloidosis, rare
Hypercalcemia (or normal corrected calcium)	Common	Absent
Hypertension	Uncommon	LCDD common Amyloidosis uncommon
Cytopenias	Anemia very common Leukopenia and thrombocytopenia, occasional	Uncommon
Immunoparesis*	Very common	Uncommon
Lytic bone lesions	Very common	Absent
Renal impairment	Common	Common
Heavy chain	IgA, IgD, IgG	None
Type of light chain	Either	Amyloid $\lambda > \kappa$ LCDD $\kappa > \lambda$
Urinary light-chain excretion	Higher	Lower

Ashley B. Irish . Comprehensive Clinical Nephrology. 5th edition, chapter 65.

Clinical Tips & Tricks
Diagnosis of Multiple Myeloma
Urine Analysis

Patient with renal impairment and lower limb edema

Not detected by dipstick

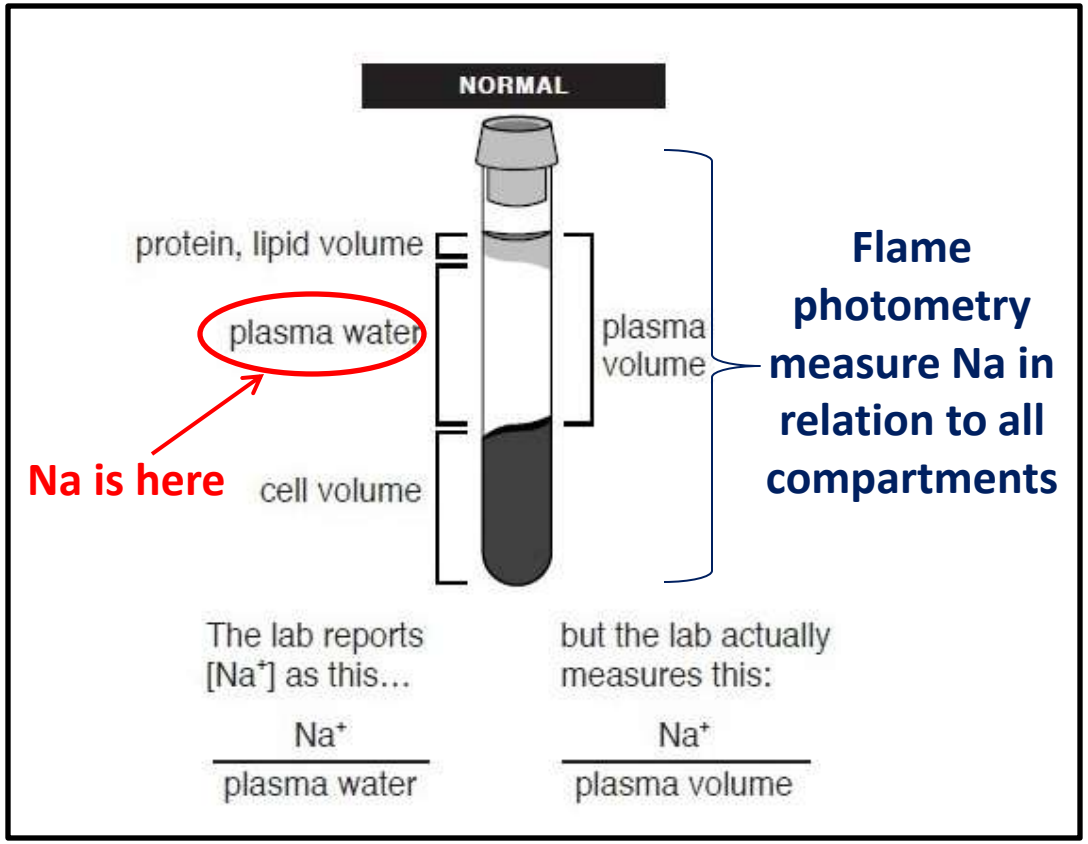
In Myeloma:
increased urinary excretion of light chains

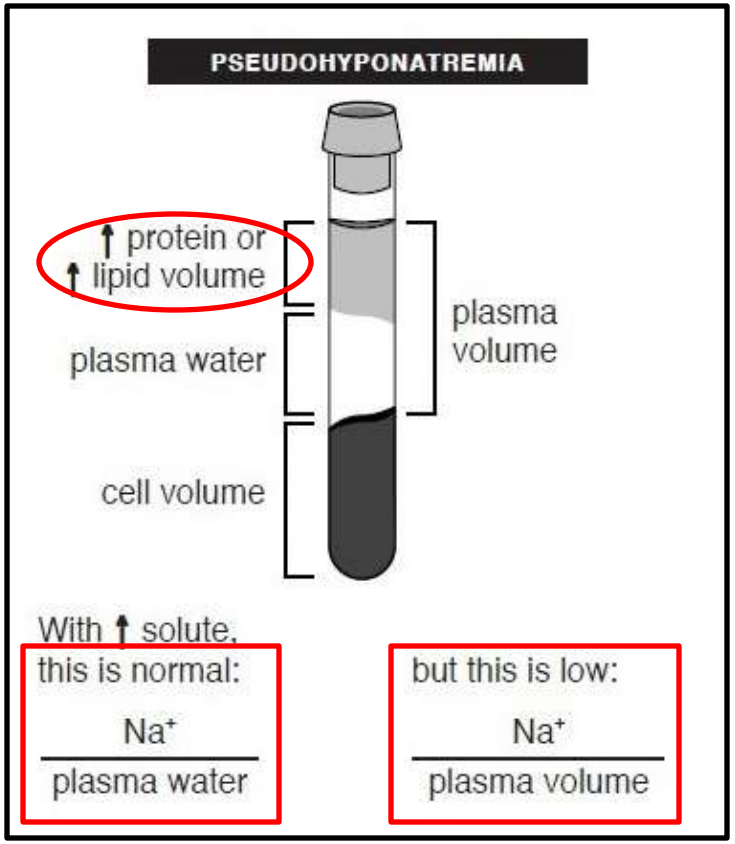
Total protein quantification or specific urine electrophoresis & immunofixation.

Clinical Tips & Tricks

Diagnosis of Multiple Myeloma

Pseudo-Hyponatremia





Clinical Tips & Tricks
Diagnosis of Multiple Myeloma
Pseudo-Hyponatremia

$$\text{Corrected Na} = \frac{\text{Serum Na} \times 93}{99 - 1.03\,(\text{triglyceride gm/L}) - 0.73\,(\text{protein gm/L})}$$

Clinical Tips & Tricks
Diagnosis of Multiple Myeloma
Pseudo-Hyponatremia

Therefore, for patients with marked elevations in plasma lipids or plasma proteins, ask the hospital laboratory to use an **ion-specific electrode** to measure the plasma sodium concentration.

A diagnosis of a plasma cell dyscrasia is not always known prior to the discovery of abnormal kidney function.

The renal biopsy, performed to identify the responsible lesion, is not infrequently the initial indication of a plasma cell dyscrasia.

Durie BG et al. Hematol J 2003;4:379.
Herrera GA et al. Arch Pathol Lab Med 2004;128:875.

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KARGER

Thank You

Gawad

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